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ORIGINAL ARTICLE

Diagnostic study and meta-analysis of C-reactive protein as a predictor of postoperative inflammatory complications after gastroesophageal cancer surgery

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Abstract
Purpose This study assessed the diagnostic accuracy of C-reactive protein (CRP) after gastroesophageal cancer resection for postoperative inflammatory complications (PIC).
Methods The clinical data and CRP values of patients operated on for gastroesophageal cancer surgery between 1997 and 2009 were retrospectively analyzed. The results of this study were compared with published data using a meta-analytic approach for diagnostic outcomes.
Results Of 210 patients included in the study, 59 developed PIC (28.1 %; 95 % CI: 22.5–34.5 %). On the postoperative day (POD) 4 and 7, CRP had the best diagnostic accuracy for PIC (AUC 0.77; 95 % CI, 0.64–0.91, AUC 0.81; 95 % CI, 0.71–0.91). Using a cut-off value of 141 mg/L (95 % CI, 131–278 mg/L) for CRP on POD 4, the sensitivity was 0.78 (95 % CI, 0.55–0.91), the specificity was 0.70 (95 % CI, 0.53–0.83) and the NPV was 0.89 (95 % CI, 0.77–0.95). The in-hospital mortality rate was 3.3 % (95 % CI, 1.5–6.9 %). In a diagnostic meta-analysis that included two additional studies, CRP had a significant predictive value after POD 3.
Conclusion There is limited evidence for the diagnostic accuracy of CRP levels for PIC after gastroesophageal cancer surgery. CRP levels on POD 4 might be useful to rule out PIC, but its diagnostic accuracy is moderate at best. For clinical routine use CRP levels are clearly not sufficient to predict PIC and have to be interpreted in the context of the whole clinical picture.

Keywords Diagnostic study · C-reactive protein · Postoperative inflammatory complications · Gastroesophageal cancer

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Introduction

Fast track surgery is slowly gaining acceptance into clinical practice; however, there are still concerns about the safety, in particular about postoperative complications after the early discharge of the patients. Especially for operations with a high postoperative complication rate, like gastroesophageal cancer surgery, this is still an issue despite a recent study with excellent results after fast-track surgery of gastric cancer [1]. Reports about morbidity and mortality after gastroesophageal cancer surgery vary significantly in the literature, with particularly higher complication rates after esophagectomy [2–4].

A laboratory value predicting, or in the case of fast track surgery reliably excluding, postoperative inflammatory complications (PIC) would be extremely helpful. Furthermore, even for patients with conventional perioperative management, early diagnosis of PIC would allow timely therapy of potentially septic patients and thus would improve their survival [5–8]. C-reactive protein (CRP), a widely used laboratory value for an acute inflammatory response [9], would be a potential candidate for such a marker. Several studies indicated that CRP can be used to predict postoperative inflammatory complications [10–12]. However, some of these studies suffer from small study sizes and lack an adequate reporting of diagnostic results.

Thus, the aim of this retrospective study was to analyze the diagnostic accuracy of CRP to detect PIC after gastroesophageal cancer surgery in an unselected patient cohort. In addition, we pooled our data with published data for a meta-analysis of diagnostic outcome data.

Patients and methods

For this retrospective study, all patients operated on for gastroesophageal cancer resection between January 1997 and December 2009 were identified from the institutional database. All patients routinely received preoperative antibiotic prophylaxis (500 mg metronidazole i.v. and 2000 mg cefamandole i.v. 60 min before the surgery) and anticoagulation with a low molecular weight heparin, according to the hospital guidelines. Some of the patients received selective digestive tract decontamination (SDD) [13, 14]: a solution of polymyxin (100 mg), tobramycin (80 mg), vancomycin (125 mg), and nystatin (500 mg) was administered orally four times a day from the morning of the day before surgery to the seventh postoperative day. Between postoperative day 5 (POD 5) and POD 7, radiological exams were routinely performed with an orally administered water-soluble contrast agent.

Data collection and definitions

The data were gathered retrospectively from the medical records. Mortality was defined as any death occurring during postoperative hospitalization. Anastomotic leakage was defined as an extravasation of the endoluminally administered water-soluble contrast agent on radiography or computed tomography or if proven during reoperation. Wound infections and intra-abdominal abscesses that were not related to anastomotic leakages, according to the diagnosis from the medical records or the operation protocols, were recorded. The presence of pneumonia was recorded when it was mentioned explicitly as a diagnosis in the medical records or as a radiological finding. Urinary infections, central line infections, *Clostridium difficile* colitides, and any other forms of infections were recorded when explicitly mentioned in the medical file, independent of the treatment. Postoperative morbidity was rated according to the classification by Dindo et al. [15]. Neoadjuvant therapy was performed according to the decision of the interdisciplinary tumor board. Tumors of the gastroesophageal junction were classified according to Siewert [16]. Type I and II tumors were considered as esophageal cancers and type III tumors as gastric cancers.

CRP measurement

The CRP concentrations were measured with an automated analytical system (Unicel DxC 800, Beckman Coulter, reference range <8 mg/L). Until August 2005, the measuring range was 3 to 300 mg/L, afterwards, the range was 1 to 500 mg/L. Therefore, CRP values exceeding 300 mg/L were reduced to 300 mg/L, and values under 3 mg/L were set to 3 mg/L.

Meta-analysis

The authors searched the National Library of Medicine (Medline) and Cochrane Library databases in March 2011 for any studies that assessed the diagnostic accuracy of CRP for any PIC following gastroesophageal cancer surgery. The reference lists of each study were searched for additional publications. Data analysis established the number of patients with and without infectious complications and the number of patients who exceeded a distinct cut-off value, which resulted in a two-by-two-table for test outcome and clinical outcome. These data were not provided explicitly in the included studies and were therefore estimated from sensitivity and specificity.

Statistical analysis and authorization

The statistical analysis was performed using R (http://www.r-project.org). Two-sided p values of less than 0.05 were considered to be statistically significant. Continuous data are expressed as the mean±standard deviation or median and interquartile range (IQR), as indicated. The chi-square test was used to compare proportions, and the Mann–Whitney test was used to compare continuous data. Generalized estimation equation models were applied for multivariate analysis of CRP levels (mean ranks) with stratification for PIC. The diagnostic accuracy was determined by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve [17]. The AUCs were computed using the nonparametric trapezoidal method and their 0.95 confidence limits (95 % CI), according to DeLong et al. [18]. The optimal cut-off values were determined by maximizing the Youden's index (=sensitivity+specificity−1). Nonparametric 95 % CIs for the cut-off values were computed with bootstrapping using the percentile method (5,000 estimates) [19]. Multivariate ROC analysis was performed with binormal ROC-generalized linear regression models with tie correction [20].

Meta-analyses of sensitivity and specificity were performed using the random effects model of DerSimonian and Laird [21]. Cochran's Q statistic was applied for the analysis of statistical heterogeneity. For each study, a diagnostic odds ratio (DOR) was calculated. The DOR is the ratio of the odds of a positive result in a patient with PIC compared to a patient without PIC: (sensitivity/(1−sensitivity))/((1−specificity)/specificity). It is a measure of the overall diagnostic accuracy and is less affected by the selected threshold and the prevalence than specificity or sensitivity alone [22].

Table 1 Distribution of inflammatory complications (*N*=210)

Any inflammatory complication	59 (28.1 %)
Including:	
Anastomotic leakage	14 (6.7 %)
Deep abscess	9 (4.3 %)
Wound infection	5 (2.4 %)
Pneumonia	13 (6.2 %)
Urinary tract infection	5 (2.4 %)
Central line infection	11 (5.2 %)
Clostridium difficile colitis	4 (1.9 %)
Other infection[a]	10 (4.8 %)

[a]Cholecystitis, pancreatitis, urogenital, and cerebral infections

The study was approved by the Swiss Federal Expert Commission for Physician Confidentiality and the state ethics review board. It was registered under www.clinicaltrials.gov/ct2/show/NCT01249534.

Results

Exclusion criteria, baseline, and outcome

A total of 221 patients operated on for gastroesophageal cancer with a clinical follow-up of at least 30 days were identified from the database. Eleven patients were excluded

Table 2 Baseline characteristics, main operation type, and clinical outcomes

		Total	Inflammatory complications		*p*
		N=210	Yes (*N*=59)	No (*N*=151)	
Age	(years)	63.3±12.2	63.6±12.9	63.2±12.0	0.505[a]
Body mass index	(kg/m^2)	24.6±4.3	25.0±4.1	24.4±4.4	0.327[a]
Gender	Male	135 (64.3 %)	40 (67.8 %)	95 (62.9 %)	0.507[b]
	Female	75 (35.7 %)	19 (32.2 %)	56 (37.1 %)	
ASA stage	I	8 (3.8 %)	4 (6.8 %)	4 (2.6 %)	0.742[a, c]
	II	132 (62.9 %)	33 (55.9 %)	99 (65.6 %)	
	III	65 (31.0 %)	21 (35.6 %)	44 (29.1 %)	
	IV	1 (0.5 %)	0 (0.0 %)	1 (0.7 %)	
	Missing data	4 (1.9 %)	1 (1.7 %)	3 (2.0 %)	
Tumor site	Gastric	152 (72.4 %)	38 (64.4 %)	114 (75.5 %)	0.106[b]
	Esophageal	58 (27.6 %)	21 (35.6 %)	37 (24.5 %)	
Neoadjuvant therapy	*N* (%)	72 (34.3 %)	16 (27.1 %)	56 (37.1 %)	0.171[b]
Selective decontamination of the digestive tract	*N* (%)	177 (84.3 %)	39 (66.1 %)	138 (91.4 %)	<0.001[b]
Main operation	Total gastrectomy	98 (46.7 %)	26 (44.1 %)	72 (47.7 %)	0.934[b]
	Transhiatal extended gastrectomy	49 (23.3 %)	13 (22.0 %)	36 (23.8 %)	
	Subtotal gastrectomy	21 (10.0 %)	6 (10.2 %)	15 (9.9 %)	
	Merendino procedure	15 (7.1 %)	6 (10.2 %)	9 (6.0 %)	
	Transmediastinal esophagectomy	11 (5.2 %)	3 (5.1 %)	8 (5.3 %)	
	Transthoracic esophagectomy	16 (7.6 %)	5 (8.5 %)	11 (7.3 %)	
Dindo classification of postoperative complications	Grade I	4 (1.9 %)	0 (0.0 %)	4 (2.6 %)	<0.001[a]
	Grade II	153 (72.9 %)	25 (42.4 %)	128 (84.8 %)	
	Grade IIIa	13 (6.2 %)	7 (11.9 %)	6 (4.0 %)	
	Grade IIIb	20 (9.5 %)	13 (22.0 %)	7 (4.6 %)	
	Grade IVa	12 (5.7 %)	8 (13.6 %)	4 (2.6 %)	
	Grade IVb	1 (0.5 %)	1 (1.7 %)	0 (0.0 %)	
	Grade V	6 (2.9 %)	5 (8.5 %)	1 (0.7 %)	
Hospitalization	(days)	27.5±15.3	37.9±21.1	23.4±9.8	<0.001[a]
Mortality	*N* (%)	7 (3.3 %)	5 (8.5 %)	2 (1.3 %)	0.009[b]

[a] Mann–Whitney test

[b] Chi-square test

[c] Analysis without missing data

Table 3 Postoperative course of the CRP levels

	Total		Inflammatory complications				p^a
			Yes		No		
	N	Med (IQR)	*N*	Med (IQR)	*N*	Med (IQR)	
CRP (mg/L)							
Preoperatively	31	4 (3–13)	8	5 (3–9)	23	4 (2–18)	0.650
POD 1	11	85 (78–133)	2	95 (84–105)[b]	9	85 (75–152)	0.906
POD 2	42	153 (99–215)	11	141 (74–190)	31	171 (100–215)	0.520
POD 3	57	179 (134–247)	19	240 (156–267)	38	167 (127–228)	0.064
POD 4	51	136 (87–248)	18	221 (139–285)	33	107 (76–157)	0.001
POD 5	51	98 (59–209)	17	177 (79–244)	34	91 (57–171)	0.065
POD 6	58	91 (57–150)	18	154 (79–225)	40	82 (53–116)	0.017
POD 7	71	91 (35–162)	25	162 (91–248)	46	61 (31–121)	<0.001
POD 8	55	60 (22–142)	21	104 (42–235)	34	45 (18–113)	0.043
POD 9	53	121 (30–174)	22	148 (109–192)	31	64 (19–153)	0.004
POD 10	48	76 (40–130)	17	96 (74–184)	31	66 (22–97)	0.036

[a]Mann–Whitney test

[b]Median (range)

because no CRP values were available. Thus, 210 patients were included in the study.

Inflammatory complications occurred in 59 of the 210 patients (28.1 %; 95 % CI, 22.5–34.5 %). An anastomotic leakage occurred in fourteen patients (6.7 %; 95 % CI, 3.9–11.0 %), diagnosed at a median of 7.0 days post-surgery (IQR, 4.0–11.3 days). Thirteen patients developed pneumonia (6.2 %; 95 % CI, 3.6–10.4 %). The distribution of the inflammatory complications is summarized in Table 1. Seven patients died during hospitalization (in-hospital mortality, 3.3 %, 95 % CI, 1.5–6.9 %).

Table 2 compares the baseline, treatment, and outcome data of the patients with and without inflammatory complications. The patients with inflammatory complications received selective digestive tract decontamination less often and had a significantly longer hospital stay and a significantly increased postoperative morbidity and mortality. As a tendency, inflammatory complications occurred more often in patients with esophageal cancer.

Postoperative course of CRP levels

On average, 2.5 CRP values were available for each patient until POD 10. Table 3 lists the median CRP levels of patients with and without inflammatory complications. Patients without inflammatory complications had the highest CRP values on POD 2 and values decreased thereafter continuously until POD 8. Patients with inflammatory complications reached their peak CRP values one day later (POD 3) but also had a continuous decrease afterwards until POD 8. From POD 3 to POD 10, CRP values of patients with inflammatory complications were clearly higher than the values from patients without inflammatory complications. This difference was statistically significant for all days except for POD 3 and 5 (p=0.064 and p=0.065). Multivariate analysis of the CRP level of patients with PIC showed that tumor site (p=0.541), neoadjuvant therapy (p=0.450) and SDD (p=0.097, tendency for lower CRP levels) have no significant influence. Similarly, for patients without PIC, neoadjuvant therapy (p=0.121) and SDD (p=0.106) had no statistically significant influence,

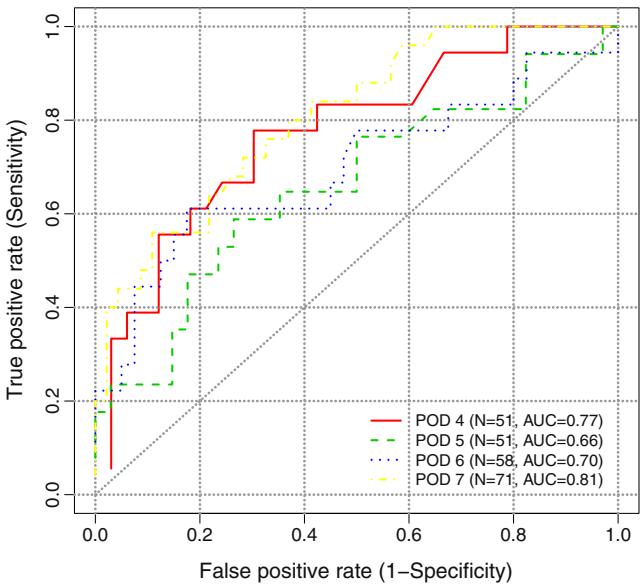

Fig. 1 Empirical ROC plots for the diagnostic accuracy of the CRP level for the detection of inflammatory complications. For the postoperative days 4–7, the sensitivity was plotted over the false positive rate (1−specificity). The greater the area under the curve (AUC), the better the diagnostic accuracy. A marker without predictive value (results by pure chance) would follow the diagonal (*gray dotted line*) and thus would have an AUC of 0.5. A perfect marker (sensitivity=1 and specificity=1 for at least one cut-off value) would have an AUC of 1

although there was a tendency to lower CRP levels. However, the tumor site had a significant influence (p=0.002), with increased CRP levels for esophageal cancer.

Diagnostic accuracy of CRP

Based on the area under the ROC curve, CRP had the best diagnostic accuracy on POD 7 (AUC 0.81, 95 % CI, 0.71–0.91) followed by POD 4 (AUC 0.77, 95 % CI, 0.64–0.91) (Fig. 1). The diagnostic outcome data of CRP for PIC are summarized in Table 4. The statistically optimal cut-off value for the CRP level on POD 4 was 141 mg/L, based on data from 51 patients. For this cut-off, the sensitivity is 78 % (14 of 18 patients with complications had a CRP value above the cut-off) and the specificity is 70 % (23 of 33 patients without complications had a CRP value below the cut-off). Figure 2 shows the dependence of sensitivity and specificity on the cut-off value for POD 4 and 7. Using the cut-off value of 141 mg/L (95 % CI, 131–278 mg/L) for POD 4 and after adjusting for the overall prevalence of 28.1 %, the positive predictive value (PPV) was 0.50 (95 % CI, 0.37–0.63), and the negative predictive value (NPV) was 0.89 (95 % CI, 0.77–0.95). When adjusting for the 25.0 % prevalence of PIC in patients with gastric cancer, the PPV was 0.46 and the NPV was 0.91 in contrast to a PPV of 0.60 and a NPV of 0.85 when adjusting for the 36.2 % prevalence of PIC in patients with esophageal cancer. In multivariate ROC analysis, the diagnostic accuracy of CRP based on the area under the ROC curve was not influenced by tumor site, neoadjuvant therapy, or SDD (p>0.05 for POD 2 to POD 10).

Meta-analysis

Three studies could be identified by a literature search for diagnostic accuracy of CRP after gastroesophageal cancer surgery [10–12]. One study had to be excluded since no diagnostic outcome data were provided [12]. The quality of reporting of the remaining two studies was not optimal; especially the number of true/false negative and positive patients was not provided. Deitmar et al. retrospectively assessed 558 patients with esophageal cancer who underwent an Ivor–Lewis esophagectomy. Anastomotic leakages occurred in 50 patients (8.9 %). The CRP levels in these 50 patients were compared to 50 randomly chosen patients without this complication [10]. Dutta et al. retrospectively analyzed the CRP levels in 136 patients who had undergone esophagogastric cancer resection (about half with gastric cancer). Fifty-four (40 %) patients developed PIC and 17 patients (12.5 %) developed an anastomotic leakage [11]. A meta-analysis for sensitivity and specificity was performed pooling the data from the studies mentioned above (Table 5) and our data (Fig. 3). The highest sensitivity was found on POD 6 (0.72; 95 % CI, 0.59–0.85), and the highest specificity occurred on

Table 4 Diagnostic accuracy of the CRP levels from POD 2 to POD 10

	N	Prev	Cut-off (mg/L) (95 % CI)	Sensitivity (95 % CI)	Specificity (95 % CI)	AUC (95 % CI)	p_{AUC}	PPV (95 % CI)	NPV (95 % CI)	TP	FN	TN	FP
POD 2	42	0.26	279 (19–284)	0.09 (0.02–0.38)	0.94 (0.79–0.98)	0.57 (0.35–0.79)	0.520	0.36 (0.23–0.51)	0.72 (0.57–0.84)	1	10	29	2
POD 3	57	0.33	201 (175–264)	0.68 (0.46–0.85)	0.66 (0.50–0.79)	0.65 (0.50–0.81)	0.064	0.44 (0.32–0.57)	0.84 (0.72–0.92)	13	6	25	13
POD 4	51	0.35	141 (131–278)	0.78 (0.55–0.91)	0.70 (0.53–0.83)	0.77 (0.64–0.91)	0.001	0.50 (0.37–0.63)	0.89 (0.77–0.95)	14	4	23	10
POD 5	51	0.33	151 (70–271)	0.59 (0.36–0.78)	0.74 (0.57–0.85)	0.66 (0.49–0.83)	0.065	0.46 (0.34–0.60)	0.82 (0.69–0.90)	10	7	25	9
POD 6	58	0.31	140 (83–195)	0.61 (0.39–0.80)	0.83 (0.68–0.91)	0.70 (0.54–0.86)	0.017	0.58 (0.45–0.70)	0.84 (0.73–0.92)	11	7	33	7
POD 7	71	0.35	162 (35–227)	0.56 (0.37–0.73)	0.89 (0.77–0.95)	0.81 (0.71–0.91)	<0.001	0.67 (0.55–0.77)	0.84 (0.73–0.91)	14	11	41	5
POD 8	55	0.38	154 (22–256)	0.43 (0.24–0.63)	0.88 (0.73–0.95)	0.66 (0.52–0.81)	0.043	0.59 (0.46–0.71)	0.80 (0.67–0.88)	9	12	30	4
POD 9	53	0.42	98 (78–144)	0.86 (0.67–0.95)	0.61 (0.44–0.76)	0.73 (0.59–0.87)	0.004	0.47 (0.34–0.60)	0.92 (0.81–0.97)	19	3	19	12
POD 10	48	0.35	73 (42–182)	0.82 (0.59–0.94)	0.55 (0.38–0.71)	0.69 (0.52–0.85)	0.036	0.42 (0.29–0.56)	0.89 (0.76–0.95)	14	3	17	14

Analysis of receiver-operating characteristic (ROC) curves for inflammatory complications

N number of patients, $Prev$ prevalence of inflammatory complications, cut-off value for maximized Youden's index, AUC area under the ROC curve, p_{AUC} p value of the AUC, PPV positive predictive value, NPV negative predictive value, PPV and NPV are adjusted for the prevalence of 28.1 % in the entire study population, TP true positive, FN false negative, TN true negative, and FP false positive cases

Cuff-off values, sensitivity, specificity, AUC, PPV, and NPV are provided with 95 % confidence intervals

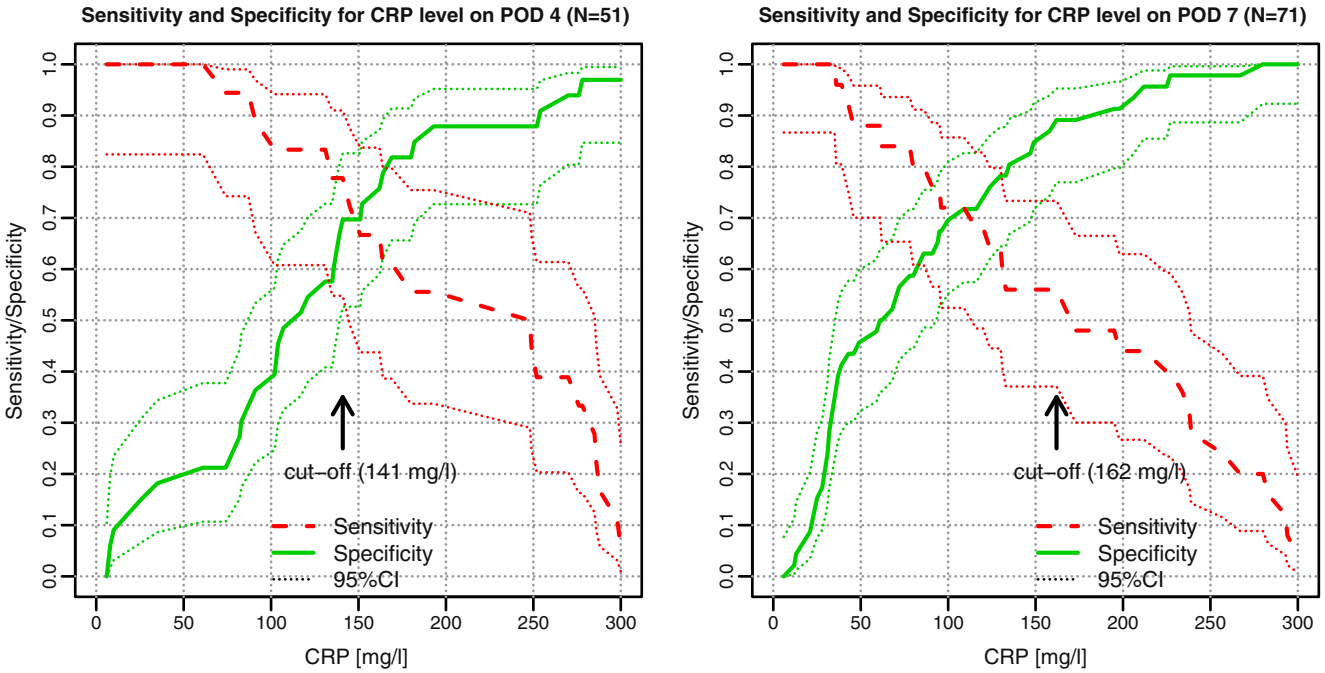

Fig. 2 Sensitivity and specificity of CRP on POD 4 and POD 7. Sensitivity (*dashed red line*) and specificity (*green line*) are plotted over all possible cut-off points. The highest Youden's index could be achieved with cut-off values of 141 mg/L for POD 4 (*arrow*) and 162 mg/L for POD 7

POD 7 (0.88; 95 % CI, 0.81–0.94). Cochran's Q statistic indicated considerable statistical heterogeneity for sensitivity and specificity on PODs 2, 3, and 4 ($p<0.001$). Finally, a meta-analysis using the diagnostic odds ratio was performed (Fig. 4). Except for POD 2 (95 % CI includes 1), the diagnostic value of CRP was statistically significant.

Discussion

This study identified the CRP level as a low to moderately performing marker for PIC from PODs 4 to 7. CRP levels before POD 4 did not have a relevant diagnostic value. A meta-analysis including two further studies confirmed CRP levels as a marker for PIC on POD 4. POD 4 is the best time point for CRP measurement to monitor the postoperative course after gastroesophageal cancer resection.

The observed morbidity and mortality in the present study is comparable with those in other reports [3, 23]. Despite conflicting reports about its efficacy, we observed a significantly decreased rate of septic complications after enteral decontamination but no change in the diagnostic accuracy of CRP [1, 14, 23]. The length of hospital stay (LOS) in our study was longer than in other reports, probably due to the reimbursement policy in Switzerland favoring long hospital stays. Nevertheless, the overall prolonged

Table 5 Data extracted for meta-analysis

Study	POD	Data extraction	AUC	Cut-off [mg/L]	n_{PIC}	$n_{No\ PIC}$	Sensitivity	Specificity
Deitmar et al. 2009 [10]	2	Graphically	0.56	135	50	50	0.92	0.20
	3	Graphically	0.59	135	50	50	0.92	0.26
	4	Graphically	0.66	135	50	50	0.86	0.46
	5	Graphically	0.74	135	50	50	0.78	0.70
	6	Graphically	0.81	135	50	50	0.76	0.86
	7	Graphically	0.77	135	50	50	0.68	0.86
Dutta et al. 2011 [11]	3	Table	0.58	180	54 [A)]	69	0.52	0.64
	4	Table	0.66	180	54 [A)]	69	0.43	0.90

[a] Thirteen patients with noninfectious complications excluded

PIC postoperative inflammatory complications

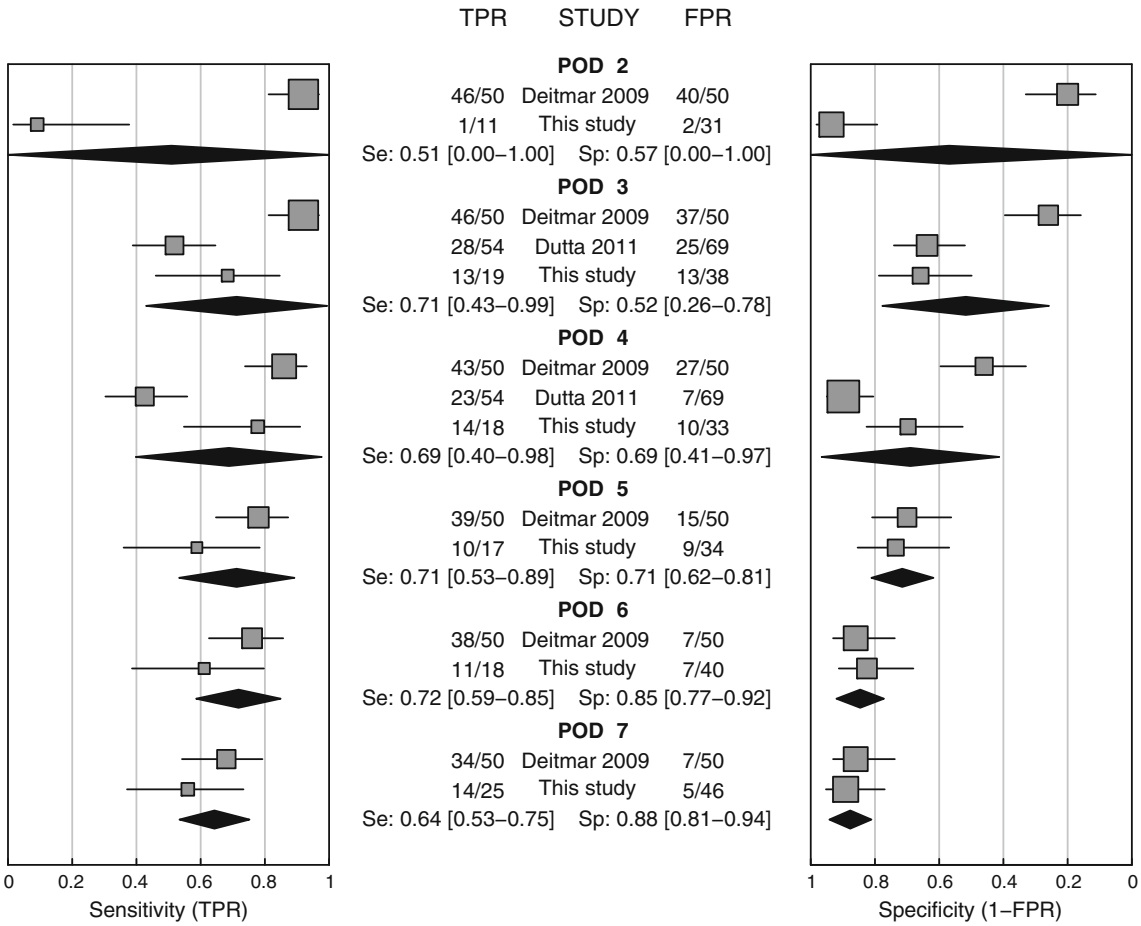

Fig. 3 Forest plot of the sensitivity and specificity of CRP levels from PODs 2 to 7. *TPR* true positive rate (=sensitivity), *FPR* false positive rate (=1−specificity). Please note inverse scale of the right plot. *Se* sensitivity, *Sp* specificity of the pooled data with 95 % confidence interval in brackets based on a random effects model

LOS may be considered advantageous because the detection rate for PIC may be higher.

The present study and meta-analysis identified CRP levels on POD 4 as the earliest time for a relevant diagnostic accuracy. Although a higher diagnostic accuracy was found at later time points, the early detection of PIC on POD 4 is clinically important for the initiation of an early goal directed therapy to improve the patients' outcomes [2, 5–8]. Furthermore, the higher diagnostic accuracy after POD 4 in the present study and the meta-analysis must be interpreted as caused by already present PIC rather than their prediction. This hypothesis is supported by Deitmar et al. [10] who demonstrated that elevated CRP levels precede anastomotic leakage after gastroesophageal surgery by 3 days. When accounting for the median occurrence of leaks at POD 7 in the present study, the diagnostic value of CRP on POD 4 is well explained. As a consequence and when accounting for the clinical context, CRP measurements should be undertaken at POD 4 for a detection of impendent complications. Elevated CRP levels on this day should be followed by further diagnostic measures like thoracic X-rays, upper gastrointestinal series, or CT scans. In case of a positive finding an early goal-directed therapy of potentially septic patients can performed, ultimately improving the patients' survival [5–8].

CRP is clearly not an optimal marker in particular since it is difficult to distinguish between patients with PIC and patients with a normal acute systemic inflammatory response caused by the operation trauma. The normal acute inflammatory response after surgery causes elevated CRP levels peaking on POD 2 followed by a decrease with a half-life of 19 h [24] as we observed in the control cohort without inflammatory complications. Furthermore, CRP levels vary considerably among patients without inflammatory complications. Thus, the optimal time point of measuring CRP is very important. Still, the diagnostic value of CRP levels was moderate at best.

Besides the optimal time for CRP measurement, the correct choice of the threshold is also of great importance. Our cut-off of 141 mg/L CRP on POD 4 corresponds well with the cut-off of Deitmar et al. (135 mg/L) [10]. Dutta et al. [11] reported a considerably higher value of 180 mg/L. All reported cut-off values were in the same range and additionally quite similar to the one (145 mg/L) reported

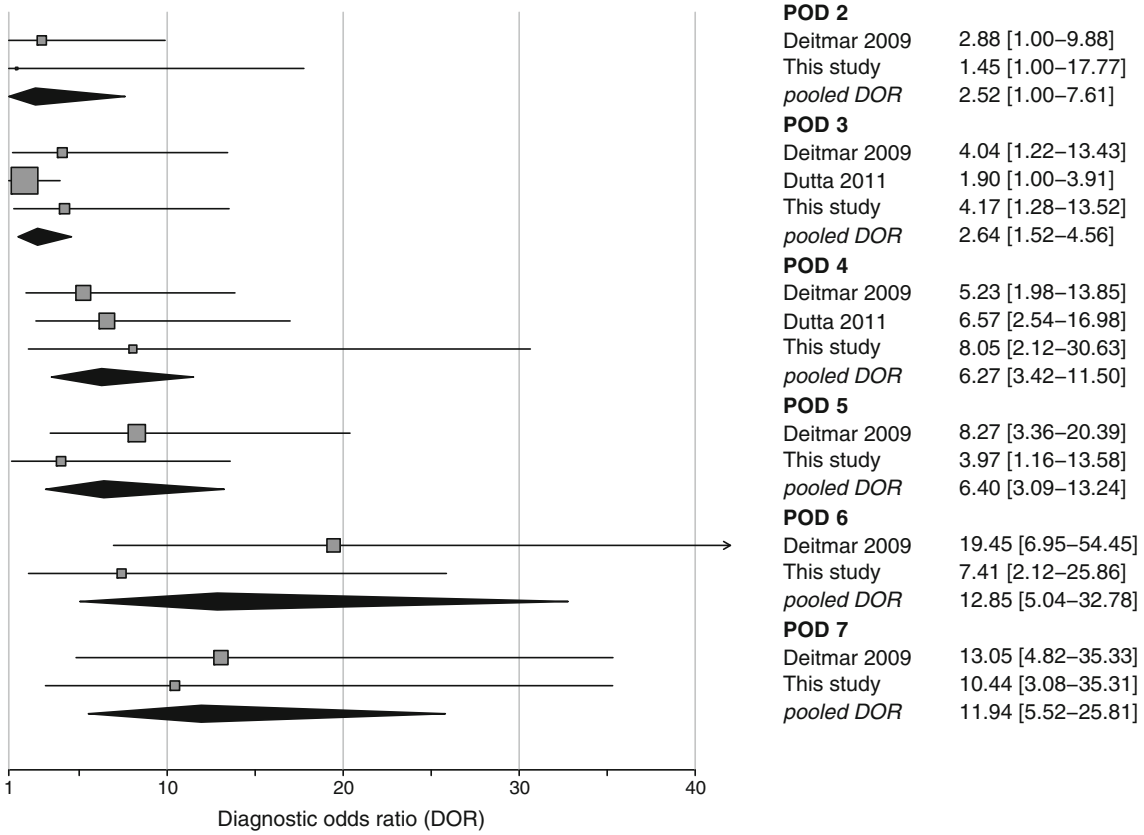

Fig. 4 Forest plot of diagnostic odds ratios for CRP from PODs 2 to 7. Diagnostic odds ratios (DOR) for CRP from PODs 2 to 7 with pooled (random effects) estimates. *Squares* represent individual studies and are provided with 95 % Cis. *Diamonds* represent the pooled diagnostic odds ratio. The size of the squares is proportional to the weight of the study

in a recent study about CRP levels after colorectal cancer resection [25]. However, as a result of heterogeneity, low sample size, and low diagnostic accuracy in our study, the confidence intervals of our cut-off values were rather large (131–278 mg/L on POD 4), thus our cut-off values can therefore not be transferred to clinical routine.

Since the selection of the cut-off value has a strong influence on sensitivity and specificity, it is difficult to compare these two values in a meta-analysis. We thus also used the diagnostic odds ratio for a meta-analysis, which is less influenced by the choice of the threshold [22]. All studies used for the meta-analysis chose the threshold by statistical optimization procedures. This approach is a compromise usually resulting in comparable sensitivity and specificity values. However, the cut-off value can also be chosen by the clinical demands.

The uncertainty of the correct cut-off value simply reflects the low to moderate diagnostic value of CRP levels. Therefore, CRP cannot be used as a "black-and-white" decision criterion that performs sufficiently well to correctly predict PIC in clinical practice. Interpretation of CRP levels must be considered in the context of the whole clinical picture. If in doubt, further diagnostic measures should be added to the clinical examination. Since the prevalence of PIC is higher after esophageal than after gastric cancer resection, elevated CRP levels have to be interpreted accordingly. The postoperative decision-making process in patients with elevated CRP levels must account for a higher likelihood of PIC after resection of esophageal cancer compared to gastric cancer.

In the last two decades, other acute phase proteins, particularly procalcitonin (PCT), were extensively investigated as markers for systemic infections [26]. One study of 40 patients after esophageal cancer resection reported PCT as a nearly perfect marker for postoperative infectious complications (AUCs of 0.97) [27]. Another study reported a significantly higher diagnostic value of PCT compared to CRP (AUCs of 0.82 versus 0.68) after cardiac surgery [28]. However, in contrast to initially encouraging results, a recent meta-analysis revealed only a low to moderate diagnostic value of PCT to discriminate patients with sepsis from patients with systemic inflammatory response syndrome [29]. Therefore, it is still questionable that PCT performs much better than CRP in the prediction of PIC. Recently, promising diagnostic values for the cytokine interleukin 6 to predict of PIC after gastric cancer resection and other major operations were reported [30, 31].

Our study has certain limitations. Although morbidity and mortality rates after esophageal and gastric cancer resection differ significantly [2–4], we pooled patients receiving either of these treatments. This pooling may have biased the diagnostic

values beside a heterogeneous patient cohort with low case numbers, even though multivariate ROC analysis did not indicate such a bias. Data were retrieved from a single center cohort over a rather long time of more than 10 years. Hence, incomplete or biased documentation particularly of the earlier cases cannot be excluded which would result in an underestimation of the inflammatory complications. Except for anastomotic leakage, the time point of initial diagnosis of inflammatory complications was not assessed. We cannot exclude the possibility of other forms of bias affecting the selection of patients or the diagnostic performance of CRP. In addition, the meta-analysis suffered from low sample size, low quality of reporting, and considerable clinical and statistical heterogeneity most likely due to the rather differing proportion of patients with gastric cancer in these studies (0–72 %).

Conclusion

CRP levels on POD 4 have a low to moderate diagnostic performance to predict inflammatory complications. Elevated CRP levels on POD 4 can also be caused by the normal postoperative inflammatory response, thus the interpretation of the CRP levels must be seen in the context of the entire clinical situation.

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